

## CLAIMS

It is claimed:

- 5 1. A water soluble polymer comprising:
- (i) a first water soluble polymer segment having at least 4 and at most about 2000 monomeric units (POLY<sub>A</sub>);
- (ii) a second water soluble segment comprising 1 to about 120 monomeric units (POLY<sub>B</sub>), which has a lower molecular weight than that of POLY<sub>A</sub> and is covalently
- 10 attached to POLY<sub>A</sub> through a linkage X; and
- (iii) a functional group, Y, attached to POLY<sub>A</sub> or POLY<sub>B</sub>;
- wherein each of POLY<sub>A</sub> and POLY<sub>B</sub> independently comprises one monomer or up to three different monomers selected from the group consisting of alkylene glycol, olefinic alcohol, vinylpyrrolidone, hydroxyalkylmethacrylamide,
- 15 hydroxyalkylmethacrylate, saccharide,  $\alpha$ -hydroxy acid, phosphazene, oxazoline, and N-acryloylmorpholine.
2. The polymer of claim 1, wherein the molecular weight of POLY<sub>A</sub> is at least twice that of POLY<sub>B</sub>.
- 20 3. The polymer of claim 1, wherein POLY<sub>A</sub> has at most about 200 monomeric units.
4. The polymer of claim 1, wherein POLY<sub>A</sub> has at most about 125 monomeric units.
- 25 5. The polymer of claim 1, wherein POLY<sub>A</sub> has at most about 25 monomeric units.
6. The polymer of claim 1, wherein said functional group is located on POLY<sub>B</sub>.
7. The polymer of claim 1, wherein POLY<sub>B</sub> comprises at least 2 monomeric units.
- 30 8. The polymer of claim 1, wherein POLY<sub>A</sub> and POLY<sub>B</sub> have the same monomeric composition.

9. The polymer of claim 1, wherein each of POLY<sub>A</sub> and POLY<sub>B</sub> is a poly(alkylene glycol).
10. The polymer of claim 11, wherein each of POLY<sub>A</sub> and POLY<sub>B</sub> is a poly(ethylene glycol).
11. The polymer of claim 1, wherein X comprises an amide linkage, a carbonate linkage, a urea linkage, or a carbamate linkage.
12. The polymer of claim 1, wherein said functional group Y comprises a nucleophilic group, selected from hydroxyl, amine, hydrazine, hydrazide, and thiol, or an electrophilic group, selected from carboxylic acid, carboxylic ester, imide ester, orthoester, carbonate, isocyanate, isothiocyanate, aldehyde, ketone, thione, alkenyl, acrylate, methacrylate, acrylamide, sulfone, maleimide, disulfide, iodo, epoxy, sulfonate, thiosulfonate, silane, alkoxy silane, halosilane, and phosphoramidate.
13. The polymer of claim 12, wherein said nucleophilic group is selected from amine, hydrazine, hydrazide, and thiol.
14. The polymer of claim 12, wherein said electrophilic group is selected from maleimide, succinimidyl ester or carbonate, benzotriazole ester or carbonate, imidazolyl ester or carbonate, glycidyl ether, vinyl sulfone, p-nitrophenyl carbonate, tresylate, acrylate, aldehyde, and orthopyridyl disulfide.
15. The polymer of claim 10, wherein the linkage X comprises a carbamate, an amide, a urea, or a carbonate, POLY<sub>A</sub> is end-capped with a capping group selected from C<sub>1</sub>-C<sub>20</sub> alkoxy, C<sub>1</sub>-C<sub>20</sub> aryloxy, and a phospholipid, and the functional group Y is attached to POLY<sub>B</sub>.
16. The polymer of claim 15, wherein the capping group is C<sub>1</sub>-C<sub>5</sub> alkoxy.

17. The polymer of claim 15, wherein the capping group is derived from distearoylphosphatidylethanolamine (DSPE).

18. The polymer of claim 15, wherein the functional group is an amine.

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19. A polymer as provided in claim 18, having the structure:



10 20. The polymer of claim 19, having a molecular weight selected from about 1000, about 5000, about 10000, and about 20000.

21. The polymer of claim 15, wherein  $\text{POLY}_A$  has a molecular weight of about 1000.

15 22. A conjugate comprising a polymer of claim 1 and a pharmacologically active agent covalently attached to the polymer.

23. The polymer of claim 10, wherein the polymer has a structure selected from:

20  $(\text{PEG}_A-\text{X}-\text{PEG}_B)_p-\text{L}-\text{Y}$  (IIa)

$(\text{PEG}_A-\text{X})_p-\text{L}-\text{PEG}_B-\text{Y}$  (IIb)

and

$(\text{PEG}_A)_p-\text{L}-\text{X}-\text{PEG}_B-\text{Y}$  (IIc)

25 wherein:

$\text{PEG}_A$  represents poly(ethylene glycol) comprising at least 4 and at most about 2000  $-\text{CH}_2\text{CH}_2\text{O}-$  monomeric units,

X is a covalent linkage,

L is a branched spacer group;

30  $\text{PEG}_B$  represents poly(ethylene glycol) comprising at least 1 and at most about 120  $-\text{CH}_2\text{CH}_2\text{O}-$  monomeric units, with the proviso that  $\text{PEG}_B$  has a lower molecular weight than that of  $\text{PEG}_A$ ;

Y is a functional group, and

p = 1 to about 100.

24. The polymer of claim 23, wherein PEG<sub>A</sub> comprises at most 200 -CH<sub>2</sub>CH<sub>2</sub>O-  
5 monomeric units.

25. The polymer of claim 23, wherein X comprises a carbamate, an amide, or a carbonate.

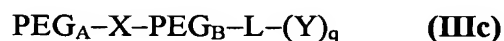
10 26. The polymer of claim 23, where p is 2 to about 10.

27. The polymer of claim 26, wherein p = 2.

28. The polymer of claim 10, wherein the polymer has a structure selected from:  
15



and



20 wherein:

PEG<sub>A</sub> represents poly(ethylene glycol) comprising at least 4 and at most about 2000  
-CH<sub>2</sub>CH<sub>2</sub>O- monomeric units,

X is a covalent linkage,

L is a branched spacer group;

25 PEG<sub>B</sub> represents poly(ethylene glycol) comprising at least 1 and at most about 120  
-CH<sub>2</sub>CH<sub>2</sub>O- monomeric units, with the proviso that PEG<sub>B</sub> has a lower molecular weight  
than that of PEG<sub>A</sub>;

Y is a functional group, and

q = 1 to about 100.

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29. The polymer of claim 28, wherein PEG<sub>A</sub> comprises at most 200 -CH<sub>2</sub>CH<sub>2</sub>O-  
monomeric units.

30. The polymer of claim 28, wherein X comprises a carbamate, an amide, or a carbonate.

31. The polymer of claim 28, where 1 is 2 to about 10.

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32. The polymer of claim 31, where 1 = 2.

33. The polymer of claim 10, wherein the polymer is a multi-arm polymer having the structure

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$$M-\{PEG_A-X-(PEG_B-Y)_q\}_x$$

wherein:

M represents a multivalent core structure;

PEG represents poly(ethylene glycol) comprising at least 4 and at most about 2000 -CH<sub>2</sub>CH<sub>2</sub>O- monomeric units;

15 X is a covalent linkage;

PEG<sub>B</sub> represents poly(ethylene glycol) comprising at least 1 and at most about 120 -CH<sub>2</sub>CH<sub>2</sub>O- monomeric units, with the proviso that PEG<sub>B</sub> has a lower molecular weight than that of PEG<sub>A</sub>;

Y is a functional group;

20 q = 1 to about 10; and

x = 3 to about 100.

34. The polymer of claim 33, wherein PEG represents poly(ethylene glycol) comprising at most 200 -CH<sub>2</sub>CH<sub>2</sub>O- monomeric units.

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35. The polymer of claim 33, wherein q = 1 or 2.

36. The polymer of claim 33, wherein M is selected from a polyol and a polyamine.

30 37. A hydrogel comprising a polymer of claim 1.

38. The hydrogel of claim 37, wherein said hydrogel is crosslinked.

39. A method of forming a water soluble polymer comprising two or more segments, said method comprising the steps of:

reacting a first water soluble polymer segment, having at least 4 and at most about 2000 monomeric units and having at least one first functional group Z, with a second

5 water soluble segment, having from 1 to about 120 monomeric units and having at least one second functional group Y', thereby forming a covalent linkage between said first and second segments by reaction of said first and second functional groups; wherein:

said second segment has a lower molecular weight than said first segment;

either said first or said second segment further comprises an additional functional  
10 group Y that is not readily reactive with either said first or said second functional group, and

each of said first and second segments independently comprises one monomer or up to three different monomers which are selected from the group consisting of alkylene glycol, olefinic alcohol, vinylpyrrolidone, hydroxyalkylmethacrylamide,

15 hydroxyalkylmethacrylate, saccharides,  $\alpha$ -hydroxy acid, vinyl alcohol, polyphosphazene, polyoxazoline, and N-acryloylmorpholine.

40. The method of claim 39, wherein each of said first and second functional groups independently comprises a group selected from amine, hydrazide, hydroxyl,

20 succinimidyl ester or carbonate, benzotriazole ester or carbonate, glycidyl ether, imidazolyl ester or carbonate, p-nitrophenyl carbonate, aldehyde, maleimide, ortho-pyridyl disulfide, acrylate, tresylate, isocyanate, and vinyl sulfone.

41. The method of claim 39, wherein said covalent linkage comprises an amide, an

25 ester, an carbamate, or a urea.

42. The method of claim 39, wherein said additional functional group comprises a group selected from hydroxyl, amine, hydrazine, hydrazide, thiol, carboxylic acid, carboxylic ester, imide ester, orthoester, carbonate, isocyanate, isothiocyanate, aldehyde, ketone,

30 thione, alkenyl, acrylate, methacrylate, acrylamide, sulfone, maleimide, disulfide, iodo, epoxy, sulfonate, thiosulfonate, tresylate, silane, alkoxysilane, halosilane, and phosphoramidate.

43. The method of claim 39, wherein said second segment comprises said additional functional group.

44. The method of claim 39, wherein each of said first and said second segments is a  
5 polyethylene glycol.

45. The method of claim 39, further comprising the step of conjugating a pharmacologically active agent to said water soluble polymer via reaction of said additional functional group Y.

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